REMARKS

Claims 1-11 are pending in the present Application. Claims 6 and 8 have been canceled, claim 1 has been amended, leaving claims 1-5, 7, and 9-11 for consideration upon entry of the present Amendment.

Claim 1 has been amended. Support for the amendment to claim 1 can be found in claims 6 and 8 as originally filed.

No new matter has been introduced by these amendments or new claim. Reconsideration and allowance of the claims are respectfully requested in view of the above amendments and the following remarks.

Claim Rejections Under 35 U.S.C. § 103(a)

Claims 1-11 stand rejected under 35 U.S.C. § 103(a), as allegedly unpatentable over Papadimitriou et al. (US 6867182) (hereinafter "Papadimitriou") in view of Yamazaki et al. (EP 0909564; cited by Applicant)(hereinafter "Yamazaki") and Cheung et al. (WO 00/61169; cited by Applicant) (hereinafter "Cheung"). (Office Action 09/22/08, page 3) Applicants respectfully traverse this rejection.

Amended Claim 1 is directed to an aqueous formulation of human erythropoietin, comprising: the human erythropoietin; a non-ionic surfactant, 0.001 to 0.1% (w/v) of a polyhydric alcohol, a neutral amino acid and 0.1 to 1.0% (w/v) of a sugar alcohol as stabilizers; an isotonic reagent; and a buffering reagent.

In making the rejection, the Examiner has stated that all of the elements parts in the instant composition are disclosed in [the cited references] and the only difference is the combination of various amounts of the ingredients into an "old well-known single composition". (OA 09/22/08, page 5) Applicants respectfully traverse the Examiner's statement regarding the present claims. "A patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex Inc.,* 127 S.Ct. 1727, 1741 (2007). To find obviousness, the Examiner must "identify a reason that would have prompted a person of ordinary skill in the art in the relevant field to combine the elements in the way the claimed new invention does." *Id.*

Papadimitriou is generally directed to a composition containing a pharmaceutically effective polypeptide [e.g. erythropoietin] and an amphiphilic compound. (Col. 2, ll. 43-50) The reference discloses that the amphiphilic compound is added to the composition under conditions

which hydrophobise the polypeptide and therefore reduces, or at least does not improve, the water-solubility of the polypeptide. (Col. 3. ll. 45-48) Papadimitriou discloses the amphiphilic compound is an anionic, zwitterionic or cationic hydrophobic surfactant, a fatty acid, an alkyl sulfonate or a lipid. (Col. 3, ll. 26-29) However, the reference does not disclose or suggest the use of a non-ionic surfactant as an integral part of the composition.

Papadimitriou discloses that auxiliary substances may be added to the composition (col. 6, line 61- col. 7, line 2), including sodium chloride, sugar alcohols such as mannitol, amino acids such as glycine or arginine, polyethylene glycol, etc. While the reference discloses that auxiliary substances may be added to the composition (col. 6, line 61- col. 7, line 2), the list of auxiliary substances provided by the reference is very broad and ranges from sugars to anti-inflammatory agents to anesthetics. As part of this list, Papadimitriou discloses the use of a sugar alcohol at a concentration of 20-100 mg/ml (2-10 w/v%) and polyethylene glycol at a concentration of 1-10% by weight. However, the reference does not provide any indication that the addition of one or more of the auxiliary substances will act to improve the long-term stability of the composition. In fact, the reference is silent with regard to the long-term stability of the aqueous composition over time. Indeed, the reference discloses that for storage purposes, the composition can be lyophilized. (Col. 2, ll. 53-54) Further, the reference does not provide any specificity as to which components would be the most useful for contributing to the stability of the composition, if any.

Specifically, the reference does not disclose the addition of non-ionic surfactant, 0.1 to 1.0% (w/v) of a sugar alcohol, and 0.001 to 0.1% w/v of a polyhydric alcohol, to an aqueous erythropoietin formulation also comprising a neutral amino acid, an isotonic reagent, and a buffering reagent, as presently claimed, for the purpose of providing long-term stability to the composition.

For at least this reason, Papadimitriou does not disclose or suggest all elements of the presently claimed invention. Since Papadimitriou does not disclose or suggest all elements of the claims, there would be no motivation to modify the reference to obtain the present claims.

Yamazaki is generally directed to a stable EPO solution preparation free from human serum albumin and gelatin and containing an amino acid selected from the group consisting of tryptophan, serine, arginine, and histidine, as a stabilizer for the EPO solution. (Paragraph [0012]) Yamazaki further discloses that the solution may also contain ingredients such as polyethylene glycol, sugar alcohols such as mannitol, inorganic salts, sulfur-containing reducing

reagents, adsorption prevention reagents such as polyoxyethylene sorbitan alkyl esters such as polysorbates 20 and 80 (paragraph [0019]), as well as phosphate buffers (paragraph [0020]).

While the reference discloses polyethylene glycol and/or mannitol as possible components in the composition, the reference does not provide any specificity with regard to the amount of each component to use to provide a composition with improved long-term stability. Specifically, the reference does not disclose the inclusion of 0.1 to 1.0% (w/v) of a sugar alcohol, and 0.001 to 0.1% w/v of a polyhydric alcohol to the composition. Even more specifically, the reference does not disclose the addition of 0.1 to 1.0% (w/v) of a sugar alcohol, and 0.001 to 0.1% w/v of a polyhydric alcohol, to an aqueous erythropoietin formulation also comprising a non-ionic surfactant, a neutral amino acid, an isotonic reagent, and a buffering reagent, as required by present Claim 1, for the purpose of providing long-term stability to the composition.

For at least these reasons, the combination of Papadimitriou, and Yamazaki does not teach or suggest all elements of the present claims and thus does not render the present claims obvious. Further, since Yamazaki does not make up for the deficiency of Papadimitriou, there would be no motivation to combine the references.

Cheung is generally directed to aqueous erythropoietin formulations free of human serum blood products and stabilized with a quantitiy of an amino acid and a sorbitan mono-9-octadecanoate poly(oxy-1,2-ethanedyl) derivative (abstract), for example polysorbate 80 and glycine as stabilizing agents (Page 4, ll. 17-18) Cheung discloses that a stabilizing amount of sorbitan mono-9-octadecanoate poly(oxy-1,2-ethanedyl) derivative is about 0.01 to about 1.0 mg/ml, and a stabilizing amount of glycine is about 0.1 g/L to 50 g/L (page 8, lines 4 and 10).

Cheung provides examples of formulations in which sodium chloride, sodium phosphate buffer, glycine and polysorbate 80 are combined with EPO. (Table A) However, the reference does not provide any examples of EPO formulations containing 0.1 to 1.0% (w/v) of a sugar alcohol, and 0.001 to 0.1% w/v of a polyhydric alcohol, in combination with a non-ionic surfactant, a neutral amino acid, an isotonic reagent, and a buffering reagent.

For at least these reasons, the combination of Papadimitriou, Yamazaki, and Cheung does not teach or suggest all elements of the present claims and thus does not render the present claims obvious. Further, since Cheung does not make up for the deficiency of Papadimitriou or Yamakazi, Applicants contend that there would be no motivation to combine the references.

Applicants have unexpectedly discovered that aqueous formulations of erythropoietin (EPO) comprising a non-ionic surfactant, 0.001 to 0.1% (w/v) of a polyhydric alcohol, a neutral

amino acid and 0.1 to 1.0% (w/v) of a sugar alcohol as stabilizers, an isotonic reagent, and a buffering reagent, are superior to formulations in which one of the foregoing elements is not present. Specifically, Applicants have unexpectedly found that the specific combination of elements provided by the EPO formulation of the present claims, prevents the adhesion of human EPO to the wall of the storage container while simultaneously preventing protein denaturation under long-term storage conditions.

Example 1 is composed of polysorbate 20, propylene glycol, glycine, sodium chloride, mannitol, phosphate buffer and EPO. Comparative Example 1 (CE1) contains EPO in a 10 mM phosphate buffer solution, while CE2 contains both EPO and polysorbate 20 in 10mM phosphate buffer. Comparative Examples 3, 4, 5, and 6, contain each of the ingredients provided in Example 1 however, in each Comparative Example, a key component has been left out of the formulation e.g. propylene glycol (CE3), glycine (CE4), sodium chloride (CE5), or mannitol (CE6). Example 1, and each of the Comparative Examples, contain 4000 IU/ml of EPO. The formulations were subjected to temperatures of either 25°C or 37°C for a period of 3 or 5 weeks, at which time the formulations were tested for the presence of EPO monomers and dimers. As provided in Table 1, the results show that following storage for 5 weeks at a temperature of 37°C, Example 1 has a recovery yield of more than 93% with no detection of dimers in the sample. In contrast, while CE1 showed no dimer formation, a significant decrease in recovery yield after 3 or 5 weeks of storage at either 25°C or 37°C was observed. Further, Comparative Examples 2-6, show the presence of dimers following incubation at 37°C, for both 3 and 5 weeks, and also demonstrate decreased recovery yield after 3 or 5 weeks at either temperature.

Thus, a synergistic effect on the stability and anti-adhesion (as measured by EPO recovery yield) of the EPO protein is provided by the specific combination of a polyhydric alcohol, a neutral amino acid, a sugar alcohol, and a non-ionic surfactant. That is, as shown in the present Examples, removal of any one of the surfactant, polyhydric alcohol, neutral amino acid, or sugar alcohol results in a marked decrease in the stability of the EPO protein.

Meanwhile, neither Papadimitriou, Yamakazi, nor Cheung provide any examples containing a neutral amino acid, a non-ionic surfactant, a polyhydric alcohol and a sugar alcohol. While these elements are broadly disclosed throughout the references, none of the references puts them all together and shows that there is a synergistic effect on the stability of the EPO protein as a result of this combination. Further, none of the references specifically discloses the inclusion of 0.1 to 1.0% (w/v) of a sugar alcohol, and 0.001 to 0.1% w/v of a polyhydric alcohol

as stabilizers. Even further, none of the references discloses that the specific combination of the components provided by the present claims results in an aqueous erythropoietin formulation having improved long-term stability, particularly when compared to formulations in which one of the claimed elements is not present. Applicants thus contend that since none of the references disclose that the combination of the elements as presently claimed results in a synergistic effect on the stability of an EPO formulation, that there would be no motivation to modify or combine the references to arrive at the present claims.

As such, even if a *prima facie* case of obviousness were conceded, which it is not, it is respectfully submitted that applicant's invention is not obvious because the particular combination of claimed elements results in unexpectedly beneficial properties. An applicant can rebut a *prima facie* case of obviousness by presenting comparative test data showing that the claimed invention possesses unexpectedly improved properties or properties that the prior art does not have. *In re Dillon*, 919 F.2d 688, 692-93, 16 U.S.P.Q.2d 1987, 1901 (Fed. Cir. 1990).

For at least these reasons, Applicants contend that the Examiner has not established a *prima facie* case of obviousness over Papadimitriou in view of Yamakazi and Cheung. Applicants respectfully request withdrawal of the obviousness rejection and an allowance of the claims.

It is believed that the foregoing amendments and remarks fully comply with the Office Action and that the claims herein should now be allowable to Applicants. Accordingly, reconsideration and allowance are requested.

If there are any additional charges with respect to this Amendment or otherwise, please charge them to Deposit Account No. 06-1130.

Respectfully submitted,

CANTOR COLBURN LLP

By_____
Sandra L. Shaner, PhD
Registration No. 47,934

By_/Lynn M. Warren Stewart/_
Lynn M. Warren Stewart
Registration No. 61,869

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CANTOR COLBURN LLP
20 Church Street, 22nd Floor
Hartford, CT 06130-3207
Telephone (860) 286-2929
Facsimile (860) 286-0115
Customer No.: 23413